

PERSONAL PRACTICE

Management of mucopolysaccharidosis type III

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The mucopolysaccharidoses are a group of inherited metabolic disorders caused by a deficiency of specific lysosomal enzymes. The enzyme deficiency results in interference with cellular function because of excessive accumulation within the cells of partially degraded glycosaminoglycans, which are also excreted to excess in the urine of affected patients.¹ Mucopolysaccharidosis (MPS) type III, or Sanfilippo's syndrome,² is characterised by the accumulation and urinary excretion of partially degraded heparan sulphate. At least four different enzyme deficiencies are known to cause the disorder.¹

Clinically the syndrome is characterised by a mild somatic phenotype combined with a severe neurodegenerative illness with prominent behavioural disturbance. Previous large clinical reviews of this condition have included many patients from small geographical areas and may not be representative of the complete clinical spectrum.^{3,4}

We present the clinical details of the 62 patients attending the special clinic for mucopolysaccharidoses at the Willink Biochemical Genetics Unit highlighting the particular problems associated with the clinical diagnosis and management of the disorder.

Patients

The clinical type and enzyme deficiency of the patients is shown in table 1. In the United Kingdom MPS IIIA is the commonest of the mucopolysaccharidoses, the exact incidence is not known with certainty, but is probably between 1:20–25 000 live births. This may be an underestimate as a number of mildly affected patients will remain undiagnosed. Type B is less common, type C is rare, and no patients with type D attend the clinic. Although the numbers involved are small, we were not able to confirm the previously reported milder clinical course associated with MPS IIIB.⁵ There appeared to be no

significant clinical differences between the different subtypes.

Presenting features

Accurate details about pregnancy and delivery were obtained for 59 of the 62 children. Three pregnancies ended prematurely at 28, 34, and 36 weeks' gestation, the infants having appropriate birth weights for the period of gestation. The other 56 pregnancies resulted in infants of normal birth weight with a mean of 3400 g and a range of 2700–4700 g. Delivery was normal in 46 cases, six followed forceps extraction, and seven were the result of caesarean section. For the majority of infants the neonatal period was uneventful (excluding those born prematurely). One patient required ventilation for meconium aspiration, but made normal progress subsequently. Five other patients were nursed briefly in the special care baby unit because of transient respiratory or feeding difficulties.

The mean age at diagnosis was 4.9 years with a range from 0.8–16 years. In six children a presymptomatic diagnosis was made after establishing the diagnosis in an older sibling. The features present at diagnosis of all the patients are shown in table 2. Most patients had a combination of developmental delay, particularly speech, and recurrent ear, nose, and throat infections. Hearing difficulties were common and a number of patients had failed health visitor screening hearing assessments.

Troublesome diarrhoea was a particular problem in 36 patients. The nature of the bowel disturbance was episodic, severe, watery motions that did not usually lead to dehydration, although many patients were admitted to hospital with a presumptive diagnosis of 'gastroenteritis'. In three patients this symptom was severe enough to lead to investigation to exclude serious bowel pathology, including sweat test and jejunal biopsy. In one patient a diagnosis of 'multiple food allergy'

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Table 1 Clinical type and enzyme deficiency of patients studied

MPS III type	Enzyme deficiency	No of patients
A	Heparan N-sulphatase	47
B	α -N-acetylglucosaminidase	12
C	Acetyl-CoA: α -glucosaminide acetyltransferase	3
D	N-acetylglucosamine-6-sulphatase	0

Table 2 Presenting features in 62 patients

Symptom	No of patients
Development delay	58
Speech delay	53
Recurrent ear, nose, and throat infections	49
Diarrhoea	36
Behaviour problems	34
Hearing loss	16

was made until the extravagant behavioural disturbance led to a reconsideration of the primary pathology. One patient was treated with pancreatic supplements for many months without appreciable affect on the bowel problem.

Twenty six patients had various ear, nose, and throat procedures performed before diagnosis. In a number of children multiple grommet insertions were felt to be necessary.

Unlike the other mucopolysaccharidoses hernias were uncommon and were present in only five children (three inguinal, two umbilical). Five children were noted to have a head circumference above the 90th centile (of these one was mistakenly diagnosed as Soto's syndrome) and only two had significant hepatomegaly at presentation.

Evolution of the phenotype

SOMATIC ABNORMALITIES (FIGS 1–3)

The clinical picture is dominated by the severe neurological disturbance, but a number of children develop other important physical signs. A coarse facial appearance develops late in the disorder, if at all, in most patients (fig 1). Stature is not significantly affected and the good physical growth associated with the behavioural disturbance accentuates the management difficulties. The exceptions are infants of Asian origin who are often very dysmorphic and hirsute despite having similar levels of residual enzyme activity (fig 2). Clinical examination in these infants often leads to a mistaken diagnosis of MPS I or II, emphasising the need for biochemical confirmation of diagnosis in all patients.



Figure 1 A white child with MPS III demonstrating a normal facial appearance.

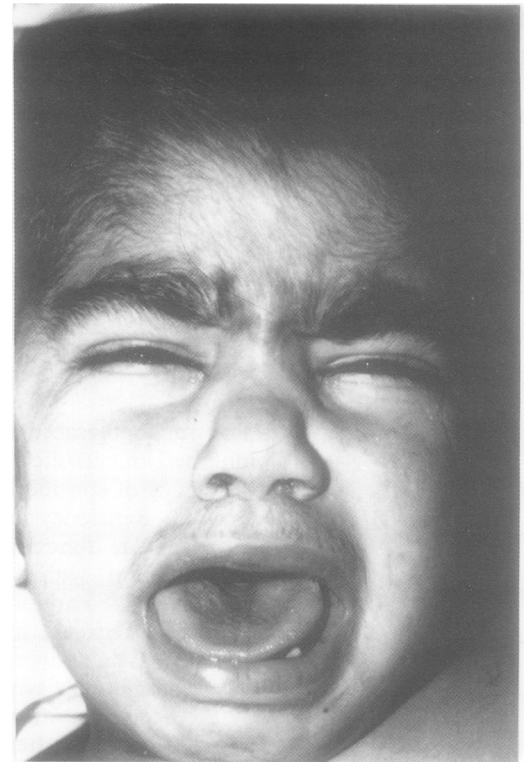


Figure 2 A child of Asian origin with MPS III demonstrating the coarse facial phenotype often associated with this ethnic group.

Cardiac abnormalities are rare. An abnormal echocardiogram was found in five patients, one of whom had coincidental dextrocardia. Only one patient had a severe cardiac lesion (hypertrophic cardiomyopathy) leading to early death. This patient with type B disease, from consanguineous Pakistani parents, had a very severe dysmorphic phenotype.

Skeletal disease is mild, but a number of patients develop dysplastic hip and pelvic changes that can be seen on radiography (fig 3). This may be associated with apparent pain and stiffness and often a diagnosis of 'Perthe's disease' is made, although the relationship between this condition and MPS III is not clear.

NEUROPSYCHIATRIC ABNORMALITIES

These can be clearly divided into three phases. Firstly, between the ages of 1 and 4 years the clinical pattern is usually one of developmental delay alone. In a number of children other features such as recurrent ear, nose, and throat

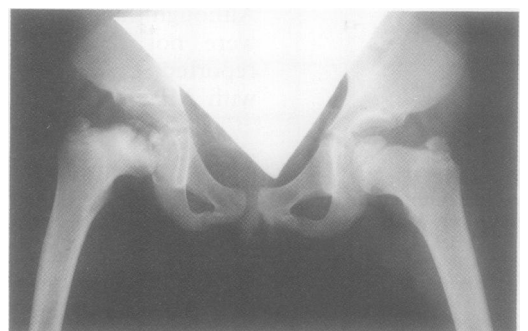


Figure 3 Radiograph of hips and pelvis of 6 year old child with MPS IIIA.

disease or bowel disturbance may dominate the clinical picture. The lack of somatic abnormality typical of mucopolysaccharidoses at this age means that this diagnosis is not usually considered. In most patients the developmental problems are most noticeable with regard to language development. Gross motor milestones are usually achieved, though these may be delayed. Fifty per cent of the affected children never completed toilet training.

The second phase of the illness, which most commonly begins around the ages of 3–4, is characterised by severe behavioural disturbance. The normal growth and good muscular strength of affected patients makes this phase of the condition the most difficult to manage. Characteristically the pattern of behaviour is heralded by increasingly frequent and severe temper tantrums. This is often followed by increasing hyperactivity and a rapid diminution in attention span. Aggression is common and many children are destructive. Panic attacks when placed in a strange environment, such as the consulting room, are usual. During this phase sleep is often severely disturbed and in some patients a reversal of the normal sleep pattern occurs. Some children appear to hallucinate at night, which leads to further behavioural disturbance and often considerable personal distress.

From the age of about 10 years the nature of the illness changes again as the children enter the third and final stage. During this quieter phase frequent falls are common as balance is lost. Feeding difficulties due to an impaired swallowing mechanism result in increasing episodes of aspiration and feed consistency has to be altered. Ultimately most children require a nasogastric tube to obtain adequate energy intake. Aspiration of saliva continues to be a problem for many children and requires separate treatment (see later).

Increasing spasticity combined with joint stiffness from the connective tissue deterioration severely impairs mobility and most children are wheelchair bound by their mid teenage years. Seizures can become troublesome during this phase. Of the patients attending the clinic, 16 developed seizures most commonly after the age of 8 years. The seizure type was generalised, tonic-clonic in all cases, although a mixed seizure type with partial seizures was noted in some.

The disorder, in common with most genetic conditions, exhibits marked heterogeneity and a number of children did not adhere to the clinical description above, in particular four patients are still independently mobile at ages 18, 20, 23, and 28 years.

Management

In the first phase of the illness attention to ear, nose, and throat problems is necessary. Unlike other mucopolysaccharidoses⁶ the milder somatic phenotype in MPS III means a much reduced anaesthetic risk and in our series many of the children underwent multiple operative procedures with no anaesthetic complications.

Special educational assessment becomes essential after diagnosis and in patients who have recurrent episodes of diarrhoea improved control can be achieved by the use of loperamide hydrochloride, 1–2 mg, up to four times a day.

Management during the second phase of the illness is extremely difficult. An approach to treatment should consider the following aspects.

SLEEP DISTURBANCE

Most affected children sleep poorly. The onset of sleep appears to be resisted and once achieved is disturbed frequently throughout the night. This produces additional parental strain as they try during the day to cope with the hyperactivity and aggressive behaviour. Hypnotic medication has a variable effect and often has to be used in high dosage in attempts to remedy this problem. Drug regimens that have had some limited success include a combination of chloral hydrate (500–1000 mg per single dose) and trimeprazine tartrate (2–3 mg kg per dose). In some children this produces paradoxical overactivity and in others rebound sedation the next day. Benzodiazepines such as temazepam (5–20 mg) or nitrazepam (5–10 mg) can be successful, but more often induce rebound sedation the next day.

Many parents use physical restraint at night utilising an elastic bed belt.* This allows the child freedom of movement within the bed, but prevents the child from getting out of bed. In some instances this has led to an improved sleep pattern. The parents sleep better knowing that the child is unable to get up and come to harm within the bedroom.

DAYTIME BEHAVIOUR

The aggression and hyperactivity respond poorly to a behavioural approach to treatment. A disciplined environment, such as within a small group at school, may lead to a temporary improvement in behaviour within that setting, but offers little practical help for the home. Drug treatment and alteration to the physical environment within the home have been most successful in allowing the family to function as near normal as possible. Most families endeavour to create a 'safe environment' for the affected child. This includes soft furnishings, toughened glass on doors and windows, wall padding, safety gates on stairs, and the removal of fragile articles. Early consideration of alterations necessary to provide for a severely physically handicapped child such as downstairs bedroom and bathroom accommodation are also important.

Drug treatment aimed at controlling the hyperactivity and aggression is necessary to allow many families to cope. The response to such treatment is very unpredictable and parents should be warned that a temporary worsening of behaviour may follow the

*Segufix Bed-Harness System, Segufix-Bandsagen Das Humane System, PO Box 50 1364, D2000 Hamburg 50, Federal Republic of Germany.

introduction of any antipsychotic agent. Thioridazine hydrochloride, starting with a small dose (12.5 mg twice a day) and gradually increasing over a period of 2–4 weeks to a maximum of 200 mg/day has been the most effective agent in our clinic. Haloperidol (0.25 mg twice a day increasing slowly to a maximum of 10 mg/day depending on effect) can also be useful. Extrapyramidal side effects are more common in children and particularly if the dose exceeds 10–15 mg/day. Chlorpromazine hydrochloride has not been a successful product in our clinic tending to induce a combination of oversedation interspersed with periods of excitability. A less satisfactory approach to drug treatment is to sedate during the day with benzodiazepines.

RESPIRE CARE

At best, drug treatment is only partially successful and early consideration must be given to respite care. The parents require adequate periods of rest to cope with the children and this usually involves organised breaks away from home. The availability of suitable respite accommodation varies tremendously throughout the country.

During the third and final stages of the disorder the child's behaviour becomes easier to manage due to increasing immobility. Different problems assume prominence and feeding difficulties as a result of swallowing incoordination begin in many patients in early teenage life. Food has to be progressively liquidised and episodes of aspiration and nasal regurgitation become more common. An inability to swallow saliva with constant choking heralds the need for nasogastric tube feeding combined with medication to inhibit saliva production. The most successful medications are hyoscine patches (placed behind the ear and replaced every three days) and benzotropine mesylate (0.25 mg twice a day increasing slowly to a maximum of 1.5 mg twice a day depending on response).

Increasing spasticity and joint stiffness lead to a wheelchair existence for many patients. Baclofen has not proved to be very successful in treating the progressive muscle stiffness, but benzodiazepines can often control painful spontaneous muscle spasms. Many parents have used non-steroidal anti-inflammatory agents to alleviate joint stiffness, but there is little evidence of therapeutic benefit.

It is often very difficult to assess the degree of pain experienced by the affected child in this stage of the illness. Episodes of mood swing with bouts of crying are very common. Most often there does not appear to be an underlying painful process responsible for these attacks and parents need to be reassured about their behavioural origin.

Seizures can be troublesome, but most respond to appropriate anticonvulsant medication. Very occasionally an unusual seizure pattern develops, such as nocturnal bouts of laughing or 'panting'.

General physical health and strength deteriorates with age and many children become wasted despite adequate energy intake. Death most commonly occurs in mid to late teenage years usually as a result of a respiratory infection complicating the severe debility. Unlike other mucopolysaccharidoses, cardiac function is preserved until very late in the illness.

The Society for Mucopolysaccharidoses Diseases has provided tremendous support for many families with affected children.†

Other possible treatments

Bone marrow transplantation has been attempted as a form of enzyme replacement in a few patients with MPS III. As with MPS I, biochemical correction is readily achieved, but the results regarding intellectual outcome have been disappointing.⁷ Transplantation has been performed on two of our patients. In one patient late rejection of the graft occurred 12 months after transplantation that was first performed at age 14 months. Retransplantation was performed but the child, now aged 4 years, shows clear evidence of developmental delay as well as some of the behavioural disturbance typical of the syndrome. The second patient was transplanted at age 10 months and at age 2 years has shown no evidence of deterioration, although this would not be expected in such a young child. A longer period of observation is necessary before one can judge the results of transplant in this patient.

It is important to remember that all of the MPS III subtypes are inherited as autosomal recessive and that first trimester prenatal diagnosis should be possible.¹

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